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10/588,444	08/04/2006	David Rekosh	00958-06	9572

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UNIVERSITY OF VIRGINIA PATENT FOUNDATION
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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,444	REKOSH ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 25-34* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-19 and 25-34* is/are rejected.

7)☒ Claim(s) *14-19 and 25-34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office acknowledges the receipt of Applicant's election and Amendment, filed on 13 July 2009. Claims 21-24 have been cancelled. New claims 26-34 have been added. Claims 1-20 and 25-34 are pending.

Election/Restriction

Applicant's election without traverse of Group III, claims 14-19 and 25-34, in the reply filed on 13 July 2009 is acknowledged.

Claims 1-13 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 13 July 2009.

Applicant's election with traverse of the species, compound 103833, in the reply filed on 13 July 2009 is acknowledged. The traversal is on the ground that compound 103833 and the other compounds share the base structure of thieno[2,3-b]pyridine. This is not found persuasive because the functional groups attached to the base structure vary substantially that the searches are not coextensive and each distinct chemical compound requires its own search and thus would be an undue burden on the Patent and Trademark Office resources due to the complex nature of the search in terms of computer time needed to perform the search and the subsequent analysis of the search results by the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-19 and 25-34 are currently examined to the extent that they read on the elected species. In order to facilitate the prosecution of this application, Applicant is requested to consider inserting a claim drawn solely to the above elected compound 103833 and canceling all non-elected embodiments from the claims.

Priority

Acknowledgement is made of Applicant's claim for priority under 35 U.S.C. 119(e) to United States Provisional Application No. 60/541,632 filed 4 February 2004. In light of the fact that the presently claimed subject matter is fully supported by the disclosure of this U.S. Provisional Application, benefit to this earlier filed U.S. Provisional Application has been granted. The effective filing date of the instant application is 4 February 2004.

Claim Objections

Claims 14-19 and 25-34 are objected to because of the following informalities:

Claims 14-19, 26-28 and 32 depend from non-elected claims.

Claims 14-19 and 25-34 are drawn, in part, to non-elected inventions.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st ¶, written description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 16-18 and 27 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings or structural chemical formulas, or by disclosure of relevant, identifying characteristics, *i.e.*, complete/partial structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, by predictability in the art, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Claims 14, 16-18 and 27 are directed to a method of inhibiting HIV replication by administering a compound identified by another method.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus. *Regents of the University of California v. Eli Lilly& Co.*, 199 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of Califomia v. Eli Lilly & Co.*, the court indicated

that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. A "representative number of species" means that the species that are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP §2163 II.A.3a.ii. Although the M.P.E.P. does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, a "compound identified by the method of claim 1" is an unspecified compound. The instant application is highly analogous to the *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). Patent is directed to a method for inhibiting prostaglandin synthesis in human host using an unspecified compound. Action by University of Rochester against G.D. Searle & Co. Inc., Monsanto Co., Pharmacia Corp., and Pfizer Inc. for patent infringement. District court granted defendants' motion for summary judgment of patent invalidity based on failure to satisfy written description and enablement requirements, and plaintiff appealed. Affirmed.

The genus of the "compound identified by the method of claim 1" is not adequately described. The specification provides description for 8 chemical compounds

and their respective analogs with disparate structures and HIV-inhibition functions (spec. pp. 34-46). However, these eight compounds and their respective analogs do not constitute a representative number of species to adequately describe such a broad genus of “compounds” because the specification does not disclose any partial structure in correlation with any biological activity that affects HIV inhibition. This is pure speculation on Applicant's part that the compounds set forth can treat any strains of HIV infection in AIDS patients. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 (written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"); *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate").

Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." M.P.E.P. §2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those species with disclosed in the examples in the present specification. The species specifically disclosed are not representative of the genus because the genus is highly variable in structures and HIV-inhibition activities, as shown by the therapeutic indexes listed in Table 5, 6 and 8 in the specification. Accordingly, it is deemed that the

specification fails to provide adequate written description for the genus in the claims and does not reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of fragment genus in the claimed invention. Thus, the claimed invention lacks an adequate written description.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (page 1115). The patent law requires that a patent contain a written description of a claimed invention independent of the requirements to enable one skilled in the art to make and use the invention. See e.g., *Invitrogen Corp. v. Clontech Labs, Inc.*, 429 F.3d 1052, 1071 n.17 (Fed. Cir. 2005) ("written description is distinct from the enablement requirement"); *Capon v. Eshhar*, 418 F.3d 1349, 1360 (Fed. Cir. 2005) ("although the legal criteria of enablement and written description are related and are often met by the same disclosure, they serve discrete legal requirements").

Claim Rejections - 35 USC § 112, 1st ¶, enablement

Claims 14-19 and 25-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragarph, the courts have put forth a series

of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id*. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Nature of the invention. Claims 14 and 16-18 are directed to a method of treating an HIV-infected subject comprising administering a compound identified by another method. Claims 15, 19, 25, 26 and 32 are directed to a method of treating an HIV-infected subject comprising administering a compound having a general base structure. Claims 27 and 33 are directed to a method of inhibiting HIV replication in a cell comprising contacting the cell with a compound identified by another method. Claims 28-31 and 34 are directed to a method of inhibiting HIV replication in a cell comprising contacting the cell with a compound having a general base structure, with as many as more than thousands of variations.

Breadth of the claims. The breadth of the claimed invention in claims 14, 16-18, 27 and 33 is exceedingly large and encompasses all unspecified compounds and treatment or inhibition of all strains of HIV in any subject or cell. Claims 14, 16-18, 27 and 33 do not provide any structural limitations whatsoever on the inhibitory compound. Thus, any chemical compound, including *inter alia*, organic compounds, peptide

mimetics, and antibodies, may be encompassed by the claims. While claims 15, 19, 25, 26 and 28-34 have some structural limitations for the genus of compounds, the present specification fails to provide adequate support for the entire scope of the claimed invention.

Working examples. The disclosure fails to provide any working embodiments that meet the claimed limitations of HIV treatment. While there are cell assay examples of the eight compounds set forth in claims 25 (spec. p. 34-46), these compounds do not share a substantial structure in correlation with the function of HIV inhibition and thus do not represent all other unspecified inhibitors that fall within the scope of the invention in claims 14, 16-18, 27 and 33. As for the method of inhibition of HIV replication in a cell, these eight compounds and their respective analogs do not even show consistent and uniform anti-HIV activity in different cell assays, as indicated by the inhibition concentrations (IC_{50}) and the therapeutic indexes (TI) for the Rev assay in luciferase reporter HeLa cell line (p.36, Table 4), the viral assay in fresh human peripheral blood mononuclear cells (p. 40, Table 5), and the reverse transcriptase assay in U1 cell culture (p. 42-46, Table 6 and 8). No *in vivo* working example of any compound is disclosed in the specification. In short, no examples are provided to evaluate the efficacy of any compound in treating AIDS.

Guidance in the specification. However, the specification fails to guide the skilled artisan toward those compounds that can reasonably be expected to retain the desired inhibitory activity of HIV replication in a cell or in a subject. The disclosure fails to provide sufficient guidance pertaining to the structural characteristics of those

compounds that are capable of inhibiting macrophage- or T cell-tropic HIV-1 isolates in a specific manner. The disclosure is silent pertaining to the identification of a common structural motif in the inhibitor compound of interest to be correlated with the inhibitory activity of HIV replication. However, without sufficient guidance pertaining to the structure-function relationship, the skilled artisan has only been extended an undue invitation to further experimentation to ascertain which compounds might function in the desired manner.

The specification provides no guidance regarding practice of the claimed method of HIV treatment. The amount of direction is limited to the cell assays of the eight compounds as set forth in claim 25. The species specifically disclosed are not representative of the genus because the genus is highly variable in structures with disparate HIV-inhibition activities, as shown by the therapeutic indexes listed in Table 5, 6 and 8 in the specification. Even for the elected embodiment of compound 103833, the 42 analogs show a wide range of TI from 0.30 to 316. Therefore, based on the experimental evidence presented in the specification, any little change in the compound structure clearly contributes to a pronounced change in the potency of the inhibitor compound, which shows a high level of unpredictability in the function of any derivative of the claimed eight compounds. Furthermore, the specification is remiss of any experimental evidence like T cell count and viral load measurement of the HIV-infected cells or subjects at different time intervals after administration of the compounds. Still further, there is no teaching of the pharmacological profile of any of the compounds to demonstrate sufficient serum half-life, bioavailability and clearance rate that are

required for the effectiveness of an AIDS therapeutic compound. Finally, there is no test to determine the cytopathic effect of and viral resistance to any of the claimed genus of compounds. The disclosure in the instant specification does not correlate with treatment of any strain and/or clade of HIV in any mammal, especially in a person.

State of the prior art and Predictability of the art. The prior art is unpredictable and fails to provide sufficient illumination pertaining to the efficacy of the claimed compounds for treating HIV infection. Most successful antiviral agents have been directed against well-characterized enzymatic or intracellular sites (Buss *et al.*, 2001; Yin *et al.*, 2006; and Greene *et al.*, 2008). However, no specific guidance is available for the specific target of interest in a HIV particle in the instant invention except for the general goal of identifying an inhibitor of Rev activity or function.

The art of HIV therapeutic development is highly unpredictable, since HIV replicates rapidly with a high mutational frequency and creates diverse 'quasi-species', which are favored by the selective pressures in the presence of inhibitors (Yin *et al.*, 2006). It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune

responses; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation, despite the high level of skill in the art.

The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage. For instance, in one anti-HIV drug evaluation study, Hendrix *et al*. (2000) report achievement of total drug concentrations but not oral absorption to an appreciable degree.

Buss and Cammack (2001) suggest the following quantifiable parameters that give information regarding the effectiveness of an antiviral drug: inhibition of the viral target enzyme; selectivity for viral versus host enzymes; inhibition of viral replication in

cell culture; ratio of efficacy to cytotoxicity in vitro; inhibition of viral replication or symptoms in an appropriate animal model of the disease; and the effect on surrogate markers, such as viral load or CD4 cell count, after administration to humans. However, the specification does not provide such information regarding the claimed compounds.

Amount of experimentation necessary. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case, there is insufficient evidence to demonstrate that those in the art would be able to use individual compounds according to the claims to treat HIV infection. Due to the highly complex and unpredictable nature of the HIV mutation, there is a large amount of undue experimentation necessary to address the many factors commonly faced by those skilled in the art such as low serum half-life, poor bioavailability, clearance of the drugs themselves (Gait, 1995, page 437), cellular uptake, transport, metabolic activation, cell-, tissue-, and organ-specific toxicity (Lee, 2003, page 14713), all of which affect the concentration of the active form of the drugs at the sites of action. Absent working examples and specific teachings of the efficacy, specificity and pharmacokinetic properties of the genus of compounds in the instant claims, those in the art would not be able to treat HIV infection or inhibit HIV replication with the claimed invention.

There is no evidence that the genus of compounds in the claimed method will actually be suitable for treating AIDS. M.P.E.P. §2164.03 [R-2] states: [I]n applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In*

re Soil, 97 F.2d 623,624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833,839, 166 USPQ 18, 24 (CCPA 1970). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488,496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991).

For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed methods.

Conclusion

No claim is allowable.

Applicant is reminded that any amendment must point to a basis in the application as filed so as not to add new matter. See MPEP §714.02 and §2163.06.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

16 September 2009